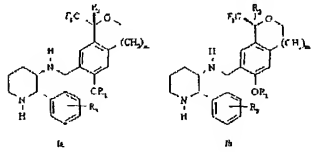
Claims

[c1]

1.A process for preparing a mixture of compounds of formulae Ia and Ib:



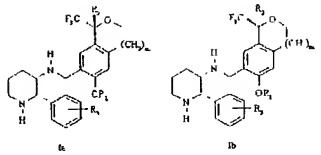
enriched in the compound of formula Ia, and pharmaceutically acceptable salts thereof,

wherein

R^1 is C_1-C_6 alkyl;
R^2 is C_1-C_6 alkyl, halo C_1-C_6 alkyl or phenyl or substituted phenyl;
R^3 is hydrogen or halo;
m is zero, one or two;

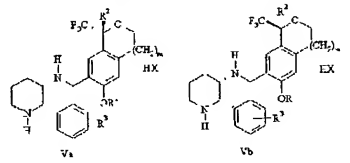
comprising the steps of

(a1) reacting a mixture of compounds of formulae Ia and Ib:



with an acid of formula HX, wherein HX is selected from the group consisting of (*S*)-(+)-mandelic acid, D-(-)-tartaric acid, di-p-toluoyl-D-tartaric acid, ((*1R*)- *endo,anti*)-(+)-3-bromocamphor-8-sulfonic acid, quinic acid, acetic acid and hydrobromic acid, to form a

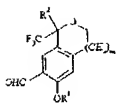
mixture of diastereomeric compounds of formulae Va and Vb, respectively:



(b1) permitting the HX salt of the diastereomeric product mixture of step (a1) to crystallize out of a solution thereof in an appropriate solvent;

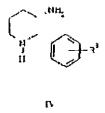
(c1) treating the resulting mixture of compounds obtained from step (b1) with a base to obtain a mixture of compounds Ia and Ib, that is enriched in the compound of formula Ia; said process further comprising the step of

reacting a compound of formula III:



II

wherein R^1 is C_1-C_6 alkyl; R^2 is C_1-C_6 alkyl, halo C_1-C_6 alkyl or phenyl or substituted phenyl; m is zero, one or two; with a compound of formula IV:



wherein R^3 is hydrogen or halo; in the presence of a reducing agent to form a mixture of diastereomeric compounds of formula Ia and Ib:

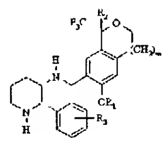
[c2] 2.A process according to claim 1 wherein the reducing agent is selected from

the group consisting of sodium triacetoxyborohydride, sodium cyanoborohydride and sodium borohydride.

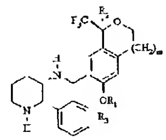
[c3] 3.A process according to claim 1wherein the reducing agent is sodium triacetoxyborohydride.

[c4]

4.A mixture of compounds of formulae Ia and Ib:



Ia



Ib

or pharmaceutically acceptable salts thereof, wherein

R^1 is C_1 -C_6 alkyl;
R^2 is C_1 -C_6 alkyl, halo C_1 -C_6 alkyl or phenyl or substituted phenyl;

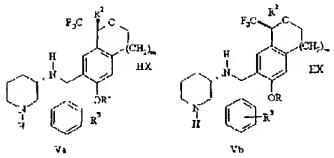
R^3 is hydrogen or halo;
m is zero, one or two;

and ratio of the compound of formula Ia to Ib is 90:10 or greater.

[c5] 5.A mixture according to claim 4 wherein the ratio is 98:2 or greater.

[c6]

6.A mixture of compounds of the formulae Va and Vb:



highly enriched in the compound of formula Va, wherein

R^1 is C_1-C_6 alkyl;

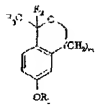
R^2 is C_1-C_6 alkyl, halo C_1-C_6 alkyl or phenyl or substituted phenyl;

R^3 is hydrogen or halo;
m is zero, one or two; wherein HX is selected from the group consisting of (*S*)-(+)-mandeli acid, D-(-)-tartaric acid, di-p-toluoyl-D-tartaric acid, ((*1R*)- *endo,anti*)-(+)-3-bromocamphor-8-sulfonic acid, quinic acid, acetic acid and hydrobromic acid.

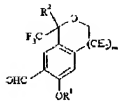
[c7] 7.A mixture according to claim 6 wherein HX is (*S*)-(+)-mandelic acid.

[c8]

8.A process according to claim 1 further comprising the step of formylating a compound of formula II:



wherein R^1 is C_1-C_6 alkyl; R^2 is C_1-C_6 alkyl, halo C_1-C_6 alkyl or phenyl or substituted phenyl; R^3 is hydrogen or halo; m is zero, one or two; via the reaction with hexamethylenetetramine in the presence of an acid to form a compound of formula III:

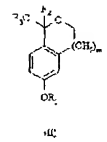


II

[c9] 9.A process according to claim 8 wherein the acid is selected from the group consisting of trifluoroacetic acid, glyceroboric acid, acetic acid and hydrochloric acid.

[c10] 10.A process according to claim 8 wherein the acid is trifluoroacetic acid.

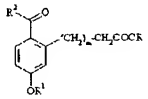
[c11] 11.A process according to claim 1 wherein the compound of formula II:



wherein R^1 is C_1-C_6 alkyl; R^2 is C_1-C_6 alkyl, halo C_1-C_6 alkyl or phenyl or

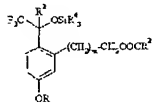
substituted phenyl; R^3 is hydrogen or halo; m is 0, 1 or 2; is prepared by a process comprising the steps of :

(a2) reacting a compound of formula VII:



VII

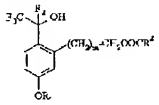
with a compound of formula $CF_3SiR^4_3$, wherein R^4 is (C_1-C_6)alkyl or phenyl, in the presence of a fluoride source to form a compound of formula VIII:



VIII

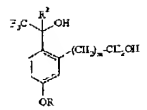
(b2) removing the silyl protecting group from the product of step (a2) via treatment with a

base or a fluoride source to form a compound of formula IX:



IX

(c2) hydrolysis of the ester group of the product of step (b2) in the presence of a base to fo a compound of formula X:



X

and (d2) performing a ring cyclization reaction on the product of step (c2) in the presence base and an activating agent selected from the group consisting of methanesulfonyl chlori methanesulfonic anhydride, *p*-toluenesulfonyl chloride, *p*-toluenesulfonic anhydride and

triflic anhydride.

[c12] 12. A process according to claim 11 wherein the fluoride source in step (a2) is selected from the group consisting of cesium fluoride, potassium fluoride and an alkylammonium fluoride.

[c13] 13.A process according to claim 11 wherein the alkylammonium fluoride is tetrabutylammonium fluoride.

[c14] 14.A process according to claim 11 wherein the fluoride source in step (a2) is cesium fluoride.

[c15] 15.A process according to claim 11 wherein the base in step (b2) is sodium hydroxide or potassium hydroxide.

[c16] 16.A process according to claim 11 wherein the preferred fluoride source of step (b2) is tetrabutylammonium fluoride, cesium fluoride, hydrofluoric acid-pyridine complex or hydrofluoric acid.

[c17] 17.A process according to claim 11 wherein the fluoride source in step (b2) is tetrabutylammonium fluoride.

[c18] 18.A process according to claim 11 wherein the base in step (c2) is selected from the group consisting of sodium hydroxide, potassium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, and potassium bicarbonate.

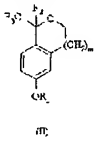
[c19] 19.A process according to claim 11 wherein the base in step (c2) is sodium hydroxide.

[c20] 20.A process according to claim 11 wherein the activating agent in step (d2) is methanesulfonyl chloride.

[c21] 21.A process according to claim 11 wherein the base for step (d2) is selected from the group consisting of triethylamine, diisopropylethylamine, 2,6-lutidine, pyridine, sodium hydroxide, potassium hydroxide, cesium carbonate and potassium carbonate.

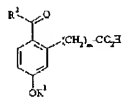
[c22] 22.A process according to claim 11 wherein the base for step (d2) is triethylamine.

[c23] 23.A process according to claim 1 wherein the compound of formula II:



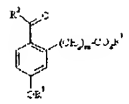
wherein R^1 is C_1-C_6 alkyl; R^2 is C_1-C_6 alkyl, halo C_1-C_6 alkyl or phenyl or substituted phenyl; R^3 is hydrogen or halo; m is 0, 1 or 2; is prepared by a method comprising the steps of :

(a3) reacting a compound of formula XI:



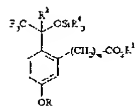
XI

with an alcohol of formula R^1OH in the presence of an acid, wherein R^1 is as defined abo to form a compound of formula XII:



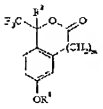
XI

(b3) reacting the product of step (a3) with compound of formula $CF_3SiR^4_3$, wherein R^4 (C_1-C_6)alkyl or phenyl, to form a compound of formula XIII:



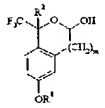
XIII

(c3) reacting the product of step (b3) with a fluoride source to obtain a lactone compound formula XIV:



XIV

(d3) reacting the lactone product of step (c3) with a reducing agent optionally in the presen of a Lewis acid to obtain a compound of formula XV:



XV

and (e3) reacting the product of step (d3) with a reducing agent in the presence of a Lewis acid.

[c24] 24. A process according to claim 23 wherein the acid of step (a3) is chosen from

the group consisting of sulfuric acid, hydrochloric acid, hydrobromic acid, trifluoroacetic acid and methanesulfonic acid.

[c25] 25.A process according to claim 23 wherein the acid of step (a3) is sulfuric acid.

[c26] 26.A process according to claim 23 wherein the fluoride source of step (b3) is selected from the group consisting of cesium fluoride, potassium fluoride, and an alkylammonium fluoride.

[c27] 27.A process according to claim 26 wherein the alkylammonium fluoride is tetrabutylammonium fluoride.

[c28] 28.A process according to claim 23 wherein the fluoride source of step (b3) is cesium fluoride.

[c29] 29.A process according to claim 23 wherein the fluoride source for step (c3) is selected from the group consisting of tetrabutylammonium fluoride, cesium fluoride, hydrofluoric acid-pyridine complex, and hydrofluoric acid.

[c30] 30.A process according to claim 23 wherein the fluoride source for step (c3) is tetrabutylammonium fluoride.

[c31] 31.A process according to claim 23 wherein the reducing agent for step (d3) is selected from the group consisting of sodium borohydride, borane tetrahydrofuran complex, borane dimethylsulfide complex, diborane, lithium borohydride, calcium borohydride, lithium aluminum hydride, diisobutylaluminum hydride, L-selectride and K-selectride.

[c32] 32.A process according to claim 23 wherein the Lewis acid for step (d3) is boron trifluoride diethyl ether complex.

[c33] 33.A process according to claim 23 wherein the reducing agent for step (e3) is triethylsilane or triphenylsilane.

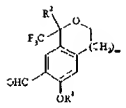
[c34] 34.A process according to claim 23 wherein the Lewis acid for step (e3) is boron trifluoride etherate or trifluoroacetic acid.

[c35] 35.A process according to claim 23 wherein the reducing agent for step (e3) is

selected from the group consisting of platinum, platinum oxide, and palladium hydroxide in the presence of hydrogen gas.

[c36]

36.A process according to claim 1 further comprising the step of purifying a compound of formula III:

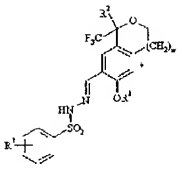


II

wherein R^1 is C_1-C_6 alkyl; R^2 is C_1-C_6 alkyl, halo C_1-C_6 alkyl or phenyl or substituted phenyl; and m is zero, one or two, comprising the steps of (a4) forming a hydrazone via the reaction of a compound of formula III with a hydrazone of formula XVI:

XVI

wherein R^1 is as defined above, in the presence of an acid to afford a compound of formu XVII:



XVII

and (b4) hydrolyzing the product of step (a4) via treatment with a reagent selected from th group consisting of copper(II) chloride, copper(II) iodide, copper(II) acetate, copper sulfate, sulfuric acid, acetic acid and hydrochloric acid.

[c37] 37.A process according to claim 36 wherein the acid in step (a4) is selected from the group consisting of acetic acid, sulfuric acid, hydrochloric acid, methanesulfonic acid and *p*-toluenesulfonic acid.

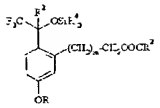
[c38] 38.A process according to claim 36 wherein the acid in step (a4) is acetic acid.

[c39] 39.A process according to claim 36 wherein the reagent for step (b4) is copper (II) chloride.

[c40]

40.A compound of formula VIII:

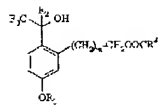
[redacted]



VIII

wherein R^1 is C_1-C_6 alkyl; R^2 is C_1-C_6 alkyl, halo C_1-C_6 alkyl or phenyl or substituted phenyl; R^4 is (C_1-C_6)alkyl or phenyl; and m is zero, one or two.

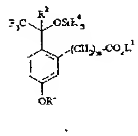
[c41] 41. A compound of formula IX:



IX

wherein R^1 is C_1-C_6 alkyl; R^2 is C_1-C_6 alkyl, halo C_1-C_6 alkyl or phenyl or substituted phenyl; and m is zero, one or two.

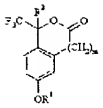
[c42] 42.A compound of formula XIII:



XIII

wherein R^1 is C_1-C_6 alkyl; R^2 is C_1-C_6 alkyl, halo C_1-C_6 alkyl or phenyl or substituted phenyl; R^4 is $(C_1$-$C_6)$alkyl or phenyl; and m is zero, one or two.

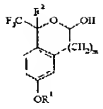
[c43] 43.A compound of formula XIV:



XIV

wherein R^1 is C_1-C_6 alkyl; R^2 is C_1-C_6 alkyl, halo C_1-C_6 alkyl or phenyl or substituted phenyl; and m is zero, one or two.

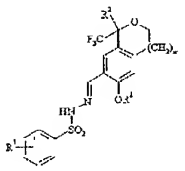
[c44] 44.A compound of formula XV:



IV

wherein R^1 is C_1-C_6 alkyl; R^2 is C_1-C_6 alkyl, halo C_1-C_6 alkyl or phenyl or substituted phenyl; and m is zero, one or two.

[c45] 45.A compound of formula XVII:



XVII

wherein R^1 is C_1-C_6 alkyl; R^2 is C_1-C_6 alkyl, halo C_1-C_6 alkyl or phenyl or substituted phenyl; and m is zero, one or two.